The Commonwealth of Massachusetts
Executive Office of Health and Human Services
Department of Public Health
William A. Hinton State Laboratory Institute
305 South Street, Jamaica Plain, MA 02130

DEVAL L. PATRICK
GOVERNOR

TIMOTHY P. MURRAY
LIEUTENANT GOVERNOR

JUDYANN BIGBY, MD
SECRETARY

JOHN AUERBACH
COMMISSIONER

Bureau of Infectious Disease Prevention, Response and Services
Division of Tuberculosis Prevention and Control

Memorandum

To: TB Health Care Providers

From: John Bernardo, M.D., Tuberculosis Medical Officer *JB*
        Sue Etkind, R.N., MS, Tuberculosis Division Director *Se*

Re: Guidelines on the use of interferon-γ release assays (IGRAs) in Massachusetts

Date: May 10, 2011

___

In 2008, the Massachusetts Medical Advisory Committee for the Elimination of Tuberculosis (MACET) published interim guidelines on the use of Interferon-γ release assays (IGRAs) to diagnose latent tuberculosis infection (LTBI). In June of 2010, the Center for Disease Prevention and Control (CDC) published formal recommendations on the use of IGRAs. http://www.cdc.gov/mmwr/pdf/rr/rr5905.pdf

The Massachusetts TB Division is in general agreement with the current CDC recommendations. The use of IGRAs can be advantageous particularly for persons born in TB endemic countries where Bacille Calmette-Guerin vaccine (BCG) is often used. However, it is our recommendation that in populations of children age < 5 years (where there are limited data on the accuracy of IGRA results), in persons with some medical conditions (including immunosuppression), and in serial testing of health care workers, use of the tuberculin skin test (TST) is the preferred testing method.

Interpretation of IGRA result should always be considered in conjunction with epidemiologic, physical and diagnostic findings. As with TST, the use of IGRA in low-risk persons is discouraged.

Attached for your information are the new guidelines. Please feel free to contact us (617-983-6970) for further information or with any questions you may have.

Guidelines for Use of Interferon-γ Release Assays (IGRAs) in Massachusetts Division of Tuberculosis Prevention and Control

May, 2011

I. Background

Tuberculin skin tests (TSTs): For decades, detection of latent TB infection (LTBI) has been based on the results of tuberculin skin testing. Purified protein derivative (PPD) used for TST is a crude mixture of many components found in *Mycobacterium tuberculosis* culture medium, which includes antigens shared with the Bacillus Calmette-Guérin vaccine (BCG). While most BCG recipients will be TST negative, some will have persistent TST positive reactions, particularly those who received repeated BCG vaccinations or who were vaccinated as an adult. TST requires 2 patient visits; the first visit to plant the TST and second visit to read the TST results.

Interferon Gamma Release Assays (IGRAs): In June 2010, CDC published guidelines on the use of IGRAs to detect *M. tuberculosis* infection (http://www.cdc.gov/mmwr/pdf/rr/rr5905.pdf). IGRAs currently approved for use in the United States by the Food and Drug Administration (FDA) for adults and children >5 years of age are the Quantiferon ®-TB Gold In-Tube test (QFT-GIT) and the T-SPOT. These tests measure the patient's immune response (interferon gamma release by lymphocytes) after stimulation of white blood cells in a test tube or on a plate with 2-3 relatively TB-specific antigens. The antigens used for the IGRA tests are not present in the BCG vaccine, so false positive tests due to BCG are unlikely to occur. The IGRA antigens are also not present in most nontuberculous mycobacteria, so false positive tests due to nontuberculous mycobacterial exposure or infection are less likely to occur with IGRAs than with TSTs.

II. Advantages and Limitations of the TST and the IGRAs

Clinical Use: There is active on-going research on the use of IGRAs. Therefore, clinical judgment based on the latest scientific evidence, with emphasis on how a given test will affect patient management, should always be used in deciding which diagnostic test to order and in interpreting test results. Similar to any other diagnostic test, the predictive value of IGRA results depends on the prevalence of *M. tuberculosis* infection in the population being tested. Each IGRA result and its interpretation should be considered in conjunction with other epidemiologic, historic, physical and diagnostic findings. As with TST, the use of IGRA in low-risk persons is discouraged.

The TST and the IGRA tests are not recommended for the diagnosis of active TB disease. Neither test can distinguish between LTBI and active disease and a negative result cannot exclude the possibility of infection or disease. Therefore, the test result should be considered in the context of the overall assessment of the patient; i.e., sputum smear microscopy and culture, radiographic evidence, exposure risk, risk of progressing to active disease, etc.

Because an assessment of the accuracy of IGRAs has been more difficult in children, CDC cautions the use of IGRAs in children aged <5 years. There are also conflicting data on the use of IGRAs in serial testing situations, as in periodic testing of health care workers. Until this is clarified, the results of IGRAs determined in a serial testing setting should be interpreted in the context of available clinical and epidemiologic information.

As with TST, live virus vaccines may affect IGRA test results. However, the effect of live virus vaccination on IGRAs has not been studied. Until additional information is available, IGRA testing in the context of live virus vaccine administration should be done either on the same day as vaccination with live-virus vaccine **OR** 4-6 weeks after the administration of the live-virus vaccine **AND** at least one month after smallpox vaccination.

Table 1: Advantages and Limitations of the TST and the IGRAs

Consideration	TST	IGRAs
Diagnosis of latent TB infection	Yes	Yes
Correlations of tests results with risk of future TB disease	>100 year of experience Lifetime risk for developing TB is known	Risk of developing TB is unknown Limited data on use of IGRA in children <5 years of age, immuno-compromised persons Conflicting data on persons for whom serial TB testing is needed
Patient encounters	2 visits (plant and read)	1 visit (blood draw)
Local health department testing capacity	Most have TST testing capacity	Phlebotomy services are not part of most local public health services
Specific handling and blood shipment requirements to the laboratory	Not Applicable	Directions for storage of materials and processing and shipping samples must be followed closely.
Cost of test*	Inexpensive	Moderately expensive
Cross-reacts with BCG, nontuberculous Mycobacteria	Yes (mostly an issue in foreign-born populations)	No
Reader bias	Reading of TST is difficult and can result in bias	Not applicable
Documentation of result	Depends on accurate recording of TST result	Laboratory test result posted

* Based on Medicaid reimbursement, the cost for TST is $7.90 as compared to $64.66 for IGRA

Public health coordination: Whenever *M. tuberculosis* infection or disease is being diagnosed by any method, the optimal approach includes coordination with local public health and the Division of Tuberculosis Prevention and Control. A positive IGRA result should prompt the same public health and medical interventions as a positive TST result.

Repeat or dual testing: There is generally no indication for following up on a positive IGRA with a TST. Routine testing of individual patients with both TST and IGRAs is not recommended.

III. IGRA Test Descriptions:

Table 2: IGRAs licensed by FDA

Quantiferon TB Gold In-Tube	T-SPOT.TB
• The Quantiferon Gold In-Tube® is the second generation of the Quantiferon ®-TB Gold test and is an enzyme-linked immunosorbent assay. • The test measures the concentration of interferon gamma in whole blood in 3 separate tubes: a nil tube (negative control), a tube containing 3 TB antigens (ESAT-6, CFP-10, and TB7.7), and a tube containing phytohemagglutinin (a mitogen used as a positive control). • Blood is drawn from the patient directly into each tube (about 1 ml of blood each), and the tubes must manage according to manufacturing instructions. • Additional information on QFT can be found at http://www.cellestis.com	• The T-SPOT.TB® is an enzyme-linked immunospot test. • The test measures the number of spots on a plate containing 4 different antigens: nil (negative control), 2 TB antigens (ESAT-6 and CFP-10), and phytohemagglutinin (positive control). • Each spot theoretically represents a white blood cell that is secreting interferon gamma. • Blood is drawn from the patient (8 ml for adults) and then must be processed in the laboratory within 8 hours. • Additional information on T-spot can be found at http://www.oxfordimmunotec.com/Why_Choose_T-SPOT_International

V. Recommendations:

A. Groups where IGRA tests are NOT recommended (TST use only)
The use of IGRAs in the following groups has not been extensively studied and/or has provided equivocal results. Until additional evidence is available, TST use is recommended for:
- Children <5 years of age
- Persons with the following medical conditions: diabetes mellitus, chronic renal failure, hematologic malignancy (e.g., leukemia and lymphomas), and other specific malignancies (carcinoma of the head or neck and lung)
- Health care workers (serial testing)

B. Groups where IGRA tests may be used: Based on the advantages and disadvantages of each test, the Massachusetts Department of Public Health, Division of Tuberculosis Prevention and Control recommends the following populations for IGRA use (with the exception of any listed in A, above):

<u>Non-U.S. Born Persons</u>
IGRAs are the preferred test for individuals who have received BCG vaccine or those who were born in TB endemic countries. List of TB endemic countries can be found at (http://www.mass.gov/dph/cdc/tb)

<u>Contact Investigations</u>
IGRA usage has been studied in a number of contact investigation situations, and a positive IGRA result generally correlates more closely with the extent of TB exposure than a positive TST. Therefore, IGRAs can be used in contact investigations **in place of** the TST. The same test (IGRAs or TST) should be used for initial and repeat (8-week post-exposure) testing of contacts.

<u>Populations that are unlikely to return for TST reading</u>
An IGRA test requires only 1 patient encounter and therefore should be considered in groups that may be unlikely to return for a repeat visit for TST reading or re-testing (e.g. homeless, substance abusers, migrant workers, etc.).

C. Groups where testing with both TST and IGRA may be considered:

<u>Immunocompromised persons</u>: Where performance of either test, IGRA or TST, may be compromised by immunosuppression, the initial use of either test format may be acceptable. Since the use of multiple tests may increase sensitivity, one might consider repeat testing using the alternative-format test if risk is identified and an initial false-negative test result is suspected.

<u>If the result of a positive TST is not believed</u>: If a patient refuses to believe the result of a given test (*e.g.*, a positive TST), follow-up testing with an alternative-format test (an IGRA) may be considered. Results of these tests and subsequent management recommendations to the patient must be considered within the context of Tb risk.

C. What should be done after a positive IGRA test or TST test ?
All persons with a positive result should be evaluated for the possibility of active TB disease. There are Massachusetts state funded TB clinics located throughout the Commonwealth. A list of TB clinics can be found at http://www.mass.gov/dph/cdc/tb

Table 5: Summary Recommendation for the use of TST and IGRA

Population Group	TST	IGRAs
BCG vaccinated or those born in TB endemic countries		x
Likely to not return for TST reading		x
Contacts	x	x

Individuals with the following medical conditions: diabetes mellitus, chronic renal failure, hematologic malignancy (e.g., leukemia and lymphomas), and other specific malignancies (carcinoma of the head or neck and lung)	X	
Children < 5 years of age	X	
Immuno-compromised persons	X	X
Health care employee (serial testing)	X	

VI. Additional Information

Reporting: Persons with positive TST or IGRA results should be reported to the Department of Public Health, Office of Integrated Surveillance and Informatics Services, as required by regulation (105 CMR 300.180 (B)). See appendix A for Latent TB Infection Reporting Form.

IGRA testing interpretation and availability:
- Quantiferon Gold in-tube http://www.cellestis.com

- T-SPOT http://www.oxfordimmunotec.com/Why_Choose_T-SPOT_International
  T-SPOT. *Service* Enquiries: Tel: +44 (0) 1235 433 164
  E-mail: t-_spot.service@oxfordimmunotec.com

TB Fact sheet and additional TB education materials are available at
http://www.mass.gov/dph/cdc/tb

Appendix A: Latent TB Infection Reporting form

Massachusetts Department of Public Health
Bureau of Communicable Disease Control
Office of Integrated Surveillance and Informatics Services
305 South Street, Room 563, Jamaica Plain, MA 02130
Phone: 617-983-6801 Confidential Fax: 617-983-6220

Received in Surveillance:
☐☐ / ☐☐ / ☐☐☐☐

Latent Tuberculosis Infection (LTBI) Reporting Form

Confidential Case Report

Last Name:

First Name:

Address:

DOB: *(mm/dd/yyyy)* ☐☐ / ☐☐ / ☐☐☐☐

Sex: M ☐ F ☐

City:

State:

Zip:

Phone Number: (☐☐☐) ☐☐☐ - ☐☐☐☐

Country of Birth: U.S. ☐   Other: ☐

Specify Other:

Date of entry into US: *(mm/dd/yyyy)* ☐☐ / ☐☐ / ☐☐☐☐

Diagnostic Information

Mantoux test (TST) administered: *(mm/dd/yyyy)* ☐☐ / ☐☐ / ☐☐☐☐

Results (mm): ☐☐

QuantiFERON Result:
☐ Positive   ☐ Indeterminate
☐ Negative   ☐ Not Done

Date: *(mm/dd/yyyy)* ☐☐ / ☐☐ / ☐☐☐☐

% Response: ☐☐☐

Risk & Treatment Information

Risk Factors:

☐ Close Contact to a person with active TB disease within the past 2 years   *Source Name:*

☐ Child 4 years of age or under

☐ Recent arrival (within past 5 years) from TB endemic country

☐ Medical risks for progressing to active TB disease:

☐ Health care worker

☐ Mycobacteria laboratory worker

☐ Resident of high risk congregate setting

Treatment Plan:

☐ Not treat ——> If not why: ☐ Pregnant ☐ Prev. Tx.   *Specify Other:*
                               ☐ ABN ALT ☐ Other

☐ Treat (On-Site)

☐ Refer for evaluation (where):

Reporting Provider: *(Last Name, First Name)*

Date Completed: *(mm/dd/yyyy)* ☐☐ / ☐☐ / ☐☐☐☐

Facility/Agency:

Phone Number: (☐☐☐) ☐☐☐ - ☐☐☐☐

Make solid marks that fit in the response boxes. Please use black or blue ink.   Right way -> A B   Wrong way -> A B

7938

Classification of tuberculin skin test reactions

≥ 5 mm considered positive for:

- Human immunodeficiency virus (HIV)-positive persons
- Recent contacts[1] of Tuberculosis (TB) case patients
- Fibrotic changes on chest radiograph consistent with prior TB
- Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of ≥ 15 mg/d of prednisone for 1 month or more)

≥ 10 mm considered positive for:

- Recent immigrant (i.e. within the past 5 years) from high prevalence countries
- Injecting drug users
- Residents and employees[2] of the following high-risk congregate settings: prisons and jails, nursing homes and other long term care facilities for the elderly, hospitals and other health-care facilities, residential facilities for patients with AIDS and homeless shelters
- Mycobacteria laboratory personnel
- Persons with the following clinical conditions that place them at high risk: silicosis, diabetes mellitus, chronic renal failure, some hematologic disorders (e.g. leukemias and lymphomas) other specific malignancies (e.g., carcinoma of the head, or neck and lungs), weight loss of ≥ 10% of ideal body weight, gastrectomy, jejunoileal bypass
- Children ≤ than 4 years of age or infants, children and adolescents exposed to adults at high-risk

≥ 15 mm considered positive for:

- Persons with no risk factors for TB

TST Conversion: An increase in reaction of ≥10 mm within 2 years should be considered a TST conversion indicative of recent infection with *M. tuberculosis*.

[1] **Contacts** are individuals who have shared air for a prolonged period of time with someone who has infectious *M. tb* (from hours to months depending on the circumstances).

[2] For persons who are otherwise at low risk and are tested at the start of employment a reaction of ≥15 mm induration is considered positive.

Medical risks for progressing from LTBI to active TB disease
- Diabetes mellitus
- Injecting drug use
- Immunosuppression
- Pulmonary fibrotic lesions
- Chronic renal failure on hemodialysis
- Gastrectomy with attendant weight loss and malabsorption
- Jejunoileal bypass, renal and cardiac transplantation, carcinoma of the head or neck
- Other neoplasms (e.g., lung cancer, leukemias and lymphomas)
- Prolonged therapy with corticosteroids and/or other immunosuppressive agents
- TNF-blocking agents, such as Remicaide® (infliximab)
- Silicosis

Reference: American Thoracic Society, Centers for Disease Control. 2000. Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection. *American Journal of Respiratory Critical Care Medicine.* Vol. 161, No. 4, Part 2.